REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, the specification has been amended to insert the attached paper copy of the substitute Sequence Listing and to insert various sequence identifiers at appropriate locations in the specification.

Further, claims 11, 14, 20, 23-25, 28, 94, 106, 113, 115, 116, 119, 121-124, 126, 146, and 149 have been canceled without prejudice or disclaimer to the subject matter recited therein. Applicant reserves the right to file one or more continuation applications(s) directed to any of the canceled subject matter.

Additionally, claims 1, 13, 22, 45, 66, 86, 135, and 141 have been amended and new claims 150-152 have been added. In particular, claims 45, 66, 86, 135, and 141 have been amended to insert the sequence identifier for the recited sequence. Claim 1 has been amended to delete the phrase "homologues," to reference the preferred fragments as defined in original claims 22 to 25, and to refer to the amino acid sequence of SEQ ID No. 2. Claim 12 has been amended to relate to a recombinant or isolated integrin heterodimer comprising an α11 subunit or fragment thereof as defined in claim 1 and a subunit β1. Support for this amendment can be found in at least originally filed claims 12-14. Claim 22 has been amended to relate to a fragment of an integrin subunit α11 as defined in claim 1 (*i.e.*, SEQ ID No.2) and to particularly define the fragments. Support for these amendments can be found in at least originally filed claims 22-25.

AMENDMENTS TO THE DRAWINGS:

Attached are replacement sheets for Figures 1-8 (13 sheets). These sheets, which include Figures 1-8, replace the original sheets for Figures 1-8. Figures 1 and 3-8 are simply better quality drawings. Figure 2 has been changed to insert the sequence identifier (SEQ. ID. No. 1) for the sequences recited therein.

New claims 150-153 have been added and relate to a pharmaceutical composition comprising as an active ingredient a recombinant or isolated integrin subunit α11 as defined in Claim 1; a recombinant or isolated integrin heterodimer as defined in Claim 13; and a fragment of an integrin subunit α11 as defined in Claim 22, respectively. Support for these new claims can be found, for example, in the abstract of the application as filed.

Lastly, replacement sheets are herewith submitted for Figures 1-8. Figure 2 has been changed to insert the sequence identifier (SEQ ID No. 1) for the corresponding nucleotide and amino acid sequence. Figure 1 and 3-8 are simply better quality drawings.

No new matter has been added by any of the present amendments to the subject application.

Turning now to the Office Action, the Examiner has indicated that the application fails to satisfy the sequence requirements since sequences on pages 9 and 21 of the specification are not included in the Sequence Listing of record. Submitted herewith is a paper copy of a substitute Sequence Listing which includes the sequences recited on pages 9 and 21 of the specification (as well as the claims). As described above, the specification and claims have been amended to recite the corresponding sequence identifiers for such sequences. A CRF of the substitute Sequence Listing is also filed concurrently herewith along with a Declaration Under 37 C.F.R. §§ 1.821-1.825. In view of the above, it is respectfully submitted that the application fully complies with the sequence requirements.

The specification, in particular Figure 2, has been objected to under 37 C.F.R. § 1.821(d) for failing to provide a sequence identifier for SEQ ID No. 1 in the

drawings. Figure 2 has been revised to include the appropriate sequence identifier. Withdrawal of this objection is therefore respectfully requested.

The Examiner has also indicated that the specification should be amended to include reference to the international and foreign applications to which benefit has herein been claimed. However, the present application (Application No. 09/980,403) is a national stage application under 35 U.S.C. § 371. Pursuant to M.P.E.P. § 1893.03(c), "it is not necessary for the applicant to amend the first sentence of the specification to reference the international application number" because "the international application is not an earlier application (it has the same filing date as the national stage) . . . ." Additionally, as to the foreign priority claim, there is no such requirement that the first line of the specification must recite the foreign priority claim. Accordingly, applicant has complied with the requirements for priority including 37 C.F.R. § 1.78. Nevertheless, applicant submits herewith an Application Data Sheet which includes the priority claims for both the international and foreign applications.

The Examiner has indicated that it is improper to recite "binding sites" in claims 11, 28, 113, 119, and 126. Applicant respectively traverses this rejection/objection. However, to expedite prosecution and not to acquiesce to the Examiner's rejection/objection, claims 11, 28, 113, 119, and 126 have been canceled without prejudice or disclaimer. This rejection/objection is therefore rendered moot.

Claims 23, 122, and 149 have been objected to under 37 C.F.R. § 1.821(d) for lacking a sequence identifier. To expedite prosecution in the present application, and not to acquiesce to the Examiner's rejection, claims 23, 122, and 149 have been

canceled. Since this objection is rendered moot, withdrawal of such objection is respectfully requested.

The Examiner has rejected claims 1, 11, 13, 14, 20, 22-25, 28, 94, 106, 113, 115, 116, 119, 121-124, 126, 146 and 149 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applications regard as the invention. There are four specific rejections (A-D) in this regard. Each of these four specific rejections is respectfully traversed.

First, concerning claims 1, 13, 22, 24, 106, 121, 123, and 124, the Examiner has indicated that recitation of "the amino acid sequence shown in SEQ ID No. 1" is indefinite since SEQ ID No. 1 is a nucleic acid sequence. SEQ ID No. 1 contains both the nucleic acid as well as the corresponding amino acid sequence. Thus, one skilled in the art would clearly understand which of the two lines in the sequence listing is the amino acid sequence shown in SEQ ID No. 1 versus the nucleic acid sequence shown in SEQ ID No. 1. However, to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, claim 1 has been amended to refer to SEQ ID No. 2, which contains the amino acid sequence only, and claims 13 and 22 have been amended to refer to the sequence defined in claim 1 (*i.e.,* SEQ ID No. 2). As discussed above, claims 24, 106, 121, 123, and 124 have been canceled without prejudice or disclaimer.

Second, the Examiner has indicated that claims 11, 22 and 28 contain improper Markush language. In accordance with the Examiner's suggestion, claim 22 has been amended. Claims 11 and 28 have been canceled without prejudice or disclaimer.

Third, with respect to claims 1, 11, 13, 20, 28, 94, 113, 119, and 126, the Examiner has stated that it is unclear whether recitation of "fragments thereof" refers to the SEQ ID No. 1 or the homologues. Applicant respectfully disagrees with the Examiner's allegation. However, to expedite prosecution of this application, and not to acquiesce to the Examiner's rejection, claims 1 and 13 have been amended such that to the term "fragment" refers to SEQ ID No. 2. Claims 11, 20, 28, 94, 113, 119 and 126 have been canceled without prejudice or disclaimer.

Fourth, concerning claims 24, 25, 123, and 124, the Examiner has indicated that the term "about" is indefinite. Applicant also respectfully disagrees with this rejection. However, to expedite prosecution of this application and not to acquiesce to the Examiner's rejection, the word "about" has been deleted from the amended claims (see amended Claim 22). As discussed above, Claims 24, 25, 123, and 124 have been canceled without prejudice or disclaimer.

In view of the above, withdrawal of the Examiner's rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Claims 1, 11, 13, 14, 20, 22-25, 28, 94, 113, 115, 116, 119, 121-124, 126, 146 and 149 have been rejected under 35 U.S.C. § 112, first paragraph, for purportedly not being enabled for the full scope of the claims.

The Examiner appears to have alleged that the description does not provide enablement for the following:

i) a recombinant or isolated integrin subunit having (*i.e.,* comprising) the amino acid fragments of SEQ ID No. 1, or homologues or fragments thereof, in claim 1;

ii) binding sites of the amino acid sequence of the integrin α11 or homologues or fragments thereof in claims 11, 14, 28, 113, 119, 126;

iii) a recombinant or isolated integrin heterodimer comprising either: a subunit α11 and any ß subunit (as in claim 115); a subunit α11 having the sequence of SEQ ID No. 1 or homologues or fragments thereof and any ß subunit (as in claim 13), or a ß1 subunit (as in claim 14);

iv) a fragment of an integrin subunit α11 having the sequence of SEQ ID No. 1, said fragment being any peptide chosen from the group comprising: peptides of the cytoplasmic domain, the I-domains and the extracellular extension region (as in claims 22 and 121); a peptide having the sequence defined in claims 23, 122 and 149; or a peptide having the sequence defined in claims 24 to 25 and 123-124;

v) a fragment of an integrin subunit α11 having the sequence of SEQ ID No. 1, said fragment being any peptide chosen from the group comprising: peptides of the cytoplasmic domain, the I-domains and the extracellular extension region (as in claims 22 and 121); a peptide having the sequence defined in claims 23, 122 and 149; or a peptide having the sequence defined in claims 24 to 25 and 123 to 124;

vi) a vaccine comprising as an active ingredient at least one member of the group consisting of an integrin heterodimer, which heterodimer comprises a subunit α11 and a subunit ß, or the subunit α11 thereof, and homologues or fragments of said integrin subunit α11, and a polynucleotide and oligonucleotide coding for said integrin subunit α11, in claims 94 and 146.

Each of these rejections is respectfully traversed and applicant addresses each one below using the roman numeral designation set forth immediately above.

Regarding rejection (i), claim 1 has been amended to relate to SEQ ID No. 2 and defined fragments thereof, and also the phrase "homologues" has been deleted. These amendments should overcome the Examiner's rejection since the Examiner has acknowledged in paragraph 13 of the Office Action that the specification is enabling for an integrin subunit α11 having the sequence of SEQ ID No. 2 and the defined fragments thereof. Claim 106 has been canceled without prejudice or disclaimer.

Regarding rejection (ii), Applicant respectfully disagrees with the Examiner's reasoning. However, to expedite prosecution of this application, and not to acquiesce to this or any other rejection, claims 11, 14, 28, 113, 119, and 126 have been canceled.

Regarding rejection (iii), claim 13 has been amended to relate to a recombinant or isolated integrin heterodimer comprising an α11 subunit as defined in claim 1 and a subunit ß1. Claims 14 and 115 have been canceled without prejudice or disclaimer. Applicant believes that the amendments obviate the rejection as the Examiner has acknowledged in paragraph 13 of the Office Action that the specification is enabling for a deterodimer comprising α11 ß1.

Regarding rejection (iv), claim 22 has been amended to relate to a fragment of an integrin subunit α11 as defined in claim 1, and to incorporate the subject matter of claims 23-25. Claims 121-124, and 149 have been canceled without prejudice or disclaimer. Applicant believes that these amendments address the rejection since the Examiner has acknowledged that the specification is enabled for a fragment *consisting of* the peptides of SEQ ID No. 2, as defined in amended claim 22 (see paragraph 13 of the Office Action).

However, applicant further believes that the specification is enabled for fragments having (*i.e., comprising)* the peptides as specified in amended claims 1 and 22. Applicant submits that a skilled person could make such a fragment comprising such peptides and test it for desired properties without undue experimentation. For example, the specification as filed provides clear guidance on how to test a peptide fragment for collagen-binding activity by chromatographic means (see, page 26, line 12 to page 27, line 8 of the specification as filed). Accepting *in arguendo* the general principle that altering the amino acid sequence of a polypeptide can alter its properties, as the Examiner has asserted, applicant respectfully submits that testing a given fragment of the integrin subunit sequence of SEQ ID No. 2 to determine whether it retains the desired properties (*e.g.,* collagen-binding activity) could readily be accomplished without undue experimentation (*see In re Wands*).

Regarding rejection (v), applicant again respectfully disagrees with the Examiner. However, without acquiescing to the Examiner's rejection, claims 94 and 146 have been canceled simply to expedite prosecution of this application.

New claims 150-152 have been introduced and are directed to a pharmaceutical composition comprising as an active ingredient a recombinant or isolated integrin subunit α11 as defined in claim 1; a recombinant or isolated integrin heterodimer as defined in claim 13; and a fragment of an integrin subunit α11 as defined in claim 22. The Examiner has acknowledged in paragraph 13 of the Office Action that the specification is enabling for such compositions.

In view of the above, the Examiner is respectfully requested to withdraw each and every one of the enablement rejections.

Additionally, claims 1, 11, 13, 14, 20, 22-25, 28, 94, 113, 115, 116, 119, 121-124, 126, 146, and 149 have been rejected under 35 U.S.C. § 112, first paragraph, for purportedly not satisfying the written description requirement. This rejection is respectfully traversed.

The Examiner has appeared to raise the same rejections in paragraph 14 of the Office Action as raised in paragraph 13 (*i.e.*, the enablement rejection). Therefore, the comments discussed above concerning the enablement rejection (including the amendments to the claims) are hereby incorporated by reference with respect to this written description rejection.

In view of the above, withdrawal of this written description rejection is respectfully requested.

Claims 1, 13, 14, 20, 94, 106, 115, 115, 116, and 146 have been rejected under 35 U.S.C. § 102(b) as supposedly being anticipated by Gullberg et al. (Dev. Dyn., 204:57-65 (1995)), as evidence by Velling et al. This rejection is respectfully traversed.

As discussed above, claims 14, 20, 94, 106, 115, 116, and 146 have been canceled without prejudice or disclaimer. Therefore, the Examiner's rejection is moot as to those claims. As to claims 1 and 13, applicant provides the following remarks.

Gullberg et al. (1995, Dev. Dyn., 204:57-65; the lead author of which is the sole inventor of the present application) describes the up-regulation of a novel integrin alpha chain, designated amount, in human fetal myotubes. This alpha subunit was identified by immunoprecipitation.

Significantly, the studies disclosed in Gullberg et al. did not extend to cloning or sequencing of the cDNA encoding amount. Thus, Gullberg et al. contains no amino acid or nucleotide sequence information. Furthermore, there is no indication from Gullberg et al. that amount is the same as the α11 integrin subunit of the present invention. In fact, no research group has ever verified the sequence of the integrin subunit in Gullberg et al. to be same as that of the α11 integrin subunit.

The Examiner has alleged that Velling et al., in particular the paragraph bridging columns 1 and 2 on page 25740, provides evidence that αmt and α11 are the same, and has concluded that SEQ. ID No. 2 of the present application is therefore inherently disclosed in Gullberg et al. Applicant strongly disagrees with this allegation.

The passage cited by the Examiner states:

> Based on similar SDS-PAGE migration patterns, **similar behaviour** under reducing conditions, association with the ß1 integrin chain, and upregulation during in vitro differentiation of human fetal myoblasts, our data show that α11 integrin is identical with αmt.

See Velling et al, column 2, paragraph 1, page 25740 (emphasis added).

Thus, the conclusions of Velling et al. are based solely on the "similar behaviour" exhibited by α11 integrin and αmt in a number of routine laboratory tests. There is no evidence in Velling et al., or indeed elsewhere, to suggest that the sequence of α11 integrin subunit of the present invention is the same as αmt. In fact, as discussed above, the *sequence* of the integrin subunit in Gullberg et al. has never been verified to be the same as α11. Velling et al. merely speculates that the proteins are the same but has no evidence to support this speculation. It is well established in the law that an anticipatory reference must be enabling and it is

equally well recognized in the law that mere speculation is insufficient without more to provide adequate enablement.

In fact, Gullberg et al. states that the αmt subunit also demonstrates behavioural similarities with integrin subunits other than α11. For instance, Gullberg et al. states:

> Attempts to perform immunoaffinity purification on anti-betal integrin columns from rat or mouse embryos will also present problem **since alpha-mt/beta1 has similar molecular weight as alpha-2/beta1 and alpha-9/beta1.**

See paragraph bridging left and right columns on page 61 of Gullberg et al. (emphasis added).

Hence, the existence of behavioural similarities does not constitute conclusive, unambiguous evidence of the identity of the αmt subunit.

In addition, it is well known in the art of molecular biology that two proteins with a similar function can have different amino acid sequences. For example, the substitution of one amino acid for another may not affect a particular function of a protein if it is a conservative substitution (*i.e.*, the replacement of lysine with arginine) or if the substitution occurs in a part of the protein that is not required for that particular function. Similarly, regions of protein sequence may tolerate the insertion or deletion of amino acids and still retain the same function.

Thus, it is quite conceivable, and is more likely to be the case, that α11 integrin and αmt, whilst appearing to share functional properties, actually have different sequences. As described on page 20, lines 2-4, of the specification as filed, α11 integrin was isolated from a uterus cDNA library. Conversely, αmt was identified in fetal muscle cells. Thus, the two integrin chains were identified in different tissue types. It is well established that tissue-specific isoforms of proteins can exist and

that these isoforms may have a similar function but differ in terms of amino acid sequence.

Therefore, even if, for the sake of argument, α11 integrin and αmt are the same protein (for which there is no evidence and which applicant strongly disputes), these two tissue-specific isoforms of the protein would be highly likely to have different amino acid sequences.

Consequently, the Examiner's allegation that SEQ ID No. 2 is inherent of the αmt integrin identified in Gullberg et al. is without foundation. There is no evidence to suggest that Gullberg et al. discloses a recombinant or isolated integrin subunit α11 having the amino acid sequence of SEQ ID No. 2 of the present application and as is claimed in claim 1. Neither is there any evidence that Gullberg et al. discloses a recombinant or isolated integrin heterodimer as is claimed in claim 13. In the absence of such evidence, applicant submits that claims 1 and 13 are novel over Gullberg et al., regardless of whether or not Velling et al. (itself not available as prior art against the present application) is considered.

Moreover, applicant submits that the subject matter of the amended claims is not rendered obvious by the teachings of Gullberg et al. It is evident from Gullberg et al. that cloning the gene encoding the integrin αmt subunit was problematic. In this regard, Gullberg et al. states:

> Further biochemical characterization of alpha-mt/beta1 **presents some problems** because of limited availability of human fetal week 10 muscle. Attempts to perform immunoaffinity purification on anti-beta1 integrin columns from rat or mouse embryos **will also present problem** since alpha-mt/beta1 has similar molecular weight as alpha-2/beta1 and alpha-9/beta1.

See paragraph bridging left and right columns on page 61 of Gullberg et al. (emphasis added).

Hence, upon reading Gullberg et al., a skilled person would not have a reasonable expectation of success of isolating the integrin αmt subunit.

Indeed, it took the present inventor (Donald Gullberg) several years to succeed in cloning the α11 gene. It is stated in Gullberg et al., which was published in 1995, that "we are currently designing methods to identify alpha-mt in a cDNA library from G6 myotubules." *See* paragraph bridging left and right columns on page 61 of Gullberg et al.

In fact, the present inventor was unable to isolate the α11 subunit using the methods disclosed in Gullberg et al. In Gullberg et al., the αmt subunit was identified by immunoprecipitation using antibodies to the ß1 integrin subunit. After publication of Gullberg et al. the present inventor attempted to isolate the α11 subunit by affinity purification using the anti-ß1 monoclonal antibody. Briefly, G6 myoblast cells were collected and differentiated in culture (which took several months of work), and a membrane preparation prepared. Affinity purification of detergent-solubilised membrane proteins was performed using the anti-ß1 monoclonal antibody coupled to a Sepharose column. Micro-sequencing of the resulting proteins revealed the presence of α2 integrin; however the α11 protein seemed to dissociate and passed through the column in the flow-through. Thus, α11 was not sequenced and could not be purified by this method.

In view of the above, the claimed invention is not anticipated by Gullberg et al. even as supposedly evidenced by Velling et al. Therefore, withdrawal of this rejection is respectfully requested.

Lastly, the Examiner has rejected claims 11, 20, 22, 28, 94, 113, 119, 121, and 126 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,686,059. This rejection is respectfully traversed.

As discussed above, Claims 11, 20, 28, 94, 113, 119, 121 and 126 have been canceled without prejudice or disclaimer. Thus, the rejection of these claims is moot. As to the Examiner's rejection as it applies to pending claim 22, applicant provides the following remarks.

Claim 22 as presently amended, relates to a fragment of an integrin subunit of SEQ ID No. 2 selected from the group consisting of a peptide from the cytoplasmic domain having the sequence KLGFFRSARRRREPGLDPTPKVLE, a peptide having the amino acid sequence of the extracellular domain, from amino acid no. 804 to amino acid no. 826 o SEQ ID No. 2, and a peptide having the amino acid sequence of the I-domain, from amino acid no. 159 to amino acid no. 355 of SEQ ID No. 2.

The Examiner has alleged that the CBS1 motif disclosed in U.S. Pat. No. 5,686,059 corresponds to amino acid residues 164 to 172 of α11 integrin. However, such a peptide does not fall within the scope of amended claim 22.

Since U.S. Pat. No. 5,686,059 neither discloses (nor even suggests) the fragments as defined in amended claim 22, withdrawal of this anticipated rejection is respectfully requested.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that the prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: March 21, 2005

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Attachments: Paper copy of substitute Sequence Listing (11 pages)
Figures 1-8 (13 replacement sheets)